Welcome to our Cold Agglutinin Disease Myth or Fact Quiz!

Begin
Question One

In cold agglutinin disease (CAD), the complement C1 complex is fixed by cold agglutinin-bound red blood cells (RBCs) and activates the classical complement pathway.
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In cold agglutinin disease (CAD), the complement C1 complex is fixed by cold agglutinin-bound red blood cells (RBCs) and activates the classical complement pathway.
Hemolysis in CAD is initiated by cold agglutinins (IgM autoantibodies) that bind RBCs at low temperatures and bind C1, activating the classical complement pathway\textsuperscript{1-3}.
The result is primarily extravascular hemolysis and some intravascular hemolysis in people with CAD\textsuperscript{1-3}.

C, complement protein; CAD, cold agglutinin disease; IgM, immunoglobulin M; RBC, red blood cell.

Complement levels in plasma of people with CAD and healthy individuals\(^1\)

Significantly lower levels of C1s in people with CAD demonstrated that the classical complement pathway is activated.

In addition, cold agglutinin titers correlate with the amount of complement deposited on the RBC in people with CAD.

C, complement protein; CAD, cold agglutinin disease; RBC, red blood cell.
Complement levels in plasma of people with CAD and healthy individuals\(^1\)

Additionally, C2 and C4 were consumed in people with CAD, providing further evidence of classical pathway activation.

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C, complement protein; CAD, cold agglutinin disease; RBC, red blood cell.
Complement levels in plasma of people with CAD and healthy individuals

Levels of C5 were not significantly different between people with CAD and healthy people, indicating the terminal pathway is not activated.

In addition, cold agglutinin titers correlate with the amount of complement deposited on the RBC in people with CAD.

C, complement protein; CAD, cold agglutinin disease; RBC, red blood cell.

Complement levels in plasma of people with CAD

Levels of C5 were not significantly different between people with CAD and healthy people, indicating the terminal pathway is not significantly altered.

In addition, cold agglutinin titers correlate with the amount of complement deposited on the RBC in people with CAD.

C, complement protein; CAD, cold agglutinin disease; RBC, red blood cell.
Summary

In CAD, the targeted complement C1 complex is fixed by cold agglutinin-bound RBCs and activates the classical complement pathway\(^1\)

In CAD, the lectin and alternative pathways remain unaffected and do not contribute to hemolysis\(^2\)

Activation of the classical complement pathway in people with CAD triggers primarily extravascular hemolysis\(^1\)

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C, complement protein; CAD, cold agglutinin disease; RBC, red blood cell.
Question Two

In a retrospective, longitudinal analysis from the Stanford Health Care of 29 patients with CAD, 65% required blood transfusions
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Anemia from CAD can be severe; most people with CAD in the Stanford Health Care study required ≥1 transfusion.1,*

**Mean transfusions per patient-year:**
11.0 (range, 0.14–79)

**Mean units of RBCs per transfusion:**
1.5 ± 1.3 (range, 1–15)

**Mean number of severe anemia events per patient-year:** 7.1

*Based on a retrospective analysis of 29 people aged ≥18 years seen at Stanford Health Care between 1995 and 2016.

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Stanford study cohort\textsuperscript{1}:

Patient journey examples

- Treatment
- Transfusion
- Mild anemia (>10g/dL)
- Moderate anemia (8.1 - 10g/dL)
- Severe anemia (<8g/dL)

Patient 54, a 48-month snapshot in the life of a CAD patient

Stanford study cohort:

Patient journey examples

- Treatment
- Transfusion
- Mild anemia (>10g/dL)
- Moderate anemia (8.1 - 10g/dL)
- Severe anemia (<8g/dL)

Patient 111, a 19-month snapshot in the life of a CAD patient

CAD, cold agglutinin disease; Dx, diagnosis; IVIG, intravenous immunoglobulin; Rx, prescription.
Stanford study cohort:

Patient journey examples

Patient 114, a 13-month snapshot in the life of a CAD patient

CAD, cold agglutinin disease; Dx, diagnosis; IVIG, intravenous immunoglobulin; Rx, prescription.
In smaller retrospective cohort studies with 4–5 years of follow-up, 40–80% of people with CAD had transfusions\textsuperscript{1–5*}

\*Study A was a population-based retrospective follow-up study of 86 people with CAD in Norway. Study B was a retrospective multicenter study of 48 people with CAD who were patients at one of three participating university centers in France over a 20-year period. Study C analyzed 33 people from July 2009 to June 2015 who attended a medical clinic in India. Study D was a Phase 2 multicenter trial to investigate the effect of a biologic drug in 20 people with CAD from October 2002 until April 2003. Study E was a retrospective analysis of 89 people with CAD identified from 1970 through 2012 who were patients at the Mayo Clinic in Minnesota.
Summary

Activation of the classical complement pathway (C1) in CAD triggers extravascular hemolysis primarily, leading to anemia\(^1\)

People with CAD have a high disease burden related to disease management and transfusions

In a retrospective Stanford Health Care study (N=29), 65% of people with CAD required \(\geq 1\) transfusion, with 11 transfusions per patient-year (mean)\(^2\)

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C, complement protein; CAD, cold agglutinin disease.
Question Three

In a recent retrospective analysis, there was no increased risk of thromboembolic events in people with CAD versus a comparison cohort of patients without CAD.
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In a recent retrospective analysis, there was no increased risk of thromboembolic events in people with CAD versus a comparison cohort of patients without CAD.
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In a recent retrospective analysis, there was no increased risk of thromboembolic events in people with CAD versus a comparison cohort of patients without CAD.
Activation of the classical complement pathway (C1) in CAD results primarily in extravascular hemolysis\(^1\)\(^-\)\(^3\)

Patients with hemolysis have been shown to have an increased incidence of TEs\(^4\)

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C, complement protein; CAD, cold agglutinin disease; TE, thromboembolic event.
Risk for TEs is increased in people with CAD versus matched controls.

Largest CAD cohort (N=814):
31% of people with CAD had TEs compared with 20% of matched controls (n=7960, \( P<0.0001 \))

*Retrospective longitudinal analysis of people enrolled in the Optum health care plans between 2006 and 2016 by assessment of de-identified records from the Optum-Humeda database, matched on gender, race, region, follow-up, age, and entry date.

CAD, cold agglutinin disease; TE, thromboembolic event.
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\(\textit{^*}\)Retrospective longitudinal analysis of people enrolled in the Optum health care plans between 2006 and 2016 by assessment of de-identified records from the Optum-Humedica database, matched on gender, race, region, follow-up, age, and entry date.
Risk for TEs is increased in people with CAD versus matched controls. 

In the same retrospective study, people with CAD also had increased risk for ≥2 types of TEs\textsuperscript{1,*}

*Retrospective longitudinal analysis of people enrolled in the Optum health care plans between 2006 and 2016 by assessment of de-identified records from the Optum-Humedica database.

\begin{tikzpicture}
\begin{axis}[
    ybar, axis on top,\]
\addplot coordinates {
    (1,18)\(\mathrm{patients\ with\ CAD}\)
    (2,14)\(\mathrm{matched\ controls}\)
};
\end{axis}
\end{tikzpicture}

\textit{P}<0.0001

\text{One type of TE}

\text{Patients (\%)}

CAD, cold agglutinin disease; TE, thromboembolic event.
In the same retrospective study, people with CAD also had increased risk for ≥2 types of TE s\textsuperscript{1,*}

*Retrospective longitudinal analysis of people enrolled in the Optum health care plans between 2006 and 2016 by assessment of de-identified records from the Optum-Humedica database.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Bar chart showing the number of patients with two or more types of thromboembolic events (TEs) among patients with CAD and matched controls.}
\end{figure}

CAD, cold agglutinin disease; TE, thromboembolic event.
Smaller retrospective cohort studies also show an increased risk of TE in people with CAD

4 out of 13 people (31%) enrolled in a Phase 2 trial experienced 7 TEs prior to treatment initiation¹

Results from a prospective, controlled, nonrandomized, multicenter Phase 2 trial with pre- and post-treatment comparison among 13 people with CAD

CAD, cold agglutinin disease; TE, thromboembolic event.
Smaller retrospective cohort studies also show an increased risk of TE in people with CAD

From 2008 to 2016, 5 out of 29 people (17%) followed at Stanford Health Care had TE²

Based on a retrospective analysis of 29 people aged ≥18 years seen at Stanford Health Care between 1995 and 2016

CAD, cold agglutinin disease; TE, thromboembolic event.
Summary

Activation of the classical complement pathway (C1) in CAD results primarily in extravascular hemolysis\(^1\)

In a recent retrospective study, compared to matched controls, people with CAD had a significantly higher risk of \(^2\):

- Thromboembolic events
- Multiple thromboembolic events
- All thromboembolic events analyzed (venous, cerebral, and arterial events)

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C, complement protein; CAD, cold agglutinin disease.
Question Four

In a recent population-based cohort study, there was **no difference** observed in the probability of survival between people with cold agglutinin disease and a matched comparison cohort 5 years after diagnosis.
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In a recent population-based cohort study, there was no difference observed in the probability of survival between people with cold agglutinin disease and a matched comparison cohort 5 years after diagnosis.
Kaplan-Meier Analysis Demonstrated Shorter Survival Probability for People With CAD

The 5-year survival probability for people with CAD after diagnosis was 61% compared with 82% for the general population matched-comparison cohort. a

People with CAD had increased mortality starting in the first year after diagnosis.

aData based on the Danish National Patient Registry, the Civil Registration System, and the Danish National Health Service Prescription Database for people with CAD identified between 1999 and 2013. Each person with CAD was matched 1:10 based on age, sex, region and adjusted based on Charlson Comorbidity Index Score, including cancer and other conditions.

CAD, cold agglutinin disease.
Kaplan-Meier Analysis Demonstrated Shorter Survival Probability for People With CAD

The 5-year survival probability for people with CAD after diagnosis was 61% compared with 82% for the general population matched-comparison cohort.\(^a\)

People with CAD had increased mortality starting in the first year after diagnosis.

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAD cohort</td>
</tr>
<tr>
<td>1</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>76%</td>
</tr>
<tr>
<td>5</td>
<td>61%</td>
</tr>
</tbody>
</table>

\(^a\)Data based on the Danish National Patient Registry, the Civil Registration System, and the Danish National Health Service Prescription Database for people with CAD identified between 1999 and 2013. Each person with CAD was matched 1:10 based on age, sex, region and adjusted based on Charlson Comorbidity Index Score, including cancer and other conditions.

CAD, cold agglutinin disease.
Increased Mortality Risk for People With CAD Versus a General Population Matched-Comparison Cohort

The highest mortality was observed within the first 5 years in people with CAD.

The adjusted HR (95% CI) for mortality in people with CAD during the first 5 years after diagnosis was 2.27 (1.32–3.89) versus the general population matched-comparison cohort.

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire follow-up period (1999–2013)</td>
<td>1.84 (1.10–3.06)</td>
<td></td>
</tr>
<tr>
<td>First 5 years after diagnosis/cohort entry</td>
<td>2.27 (1.32–3.89)</td>
<td></td>
</tr>
</tbody>
</table>

aData based on the Danish National Patient Registry, the Civil Registration System, and the Danish National Health Service Prescription Database for people with CAD identified between 1999 and 2013. Each person with CAD was matched 1:10 based on age, sex, region and adjusted based on Charlson Comorbidity Index Score, including cancer and other conditions.

bAdjusted based on Charlson Comorbidity Index score.

cAD, cold agglutinin disease.

Thank you for taking our Myth and Fact Quiz

Lastly, do you think this has improved your knowledge of cold agglutinin disease?

- YES
- NO